REMARKS

In the Specification:

The Examiner objected to the disclosure because it contains embedded hyperlinks and/or other forms of browser-executable code. The Examiner has stated that under MPEP § 608.01, Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. Per the Examiner's request, and in compliance with MPEP § 608.01, Applicant has deleted the embedded hyperlinks and/or other forms of browser-executable code. Therefore, Applicant respectfully requests that the Examiner withdraw this ground of objection.

The Examiner also objected to the disclosure, alleging that the tables are not labeled consecutively. Specifically, the Examiner contends that the first table is Table 6 on page 61. Applicant respectfully disagrees and directs the Examiner's attention to Table 1, beginning on page 34 and running through page 50 of the instant application. Table 2 appears on page 51, Table 3 on page 52, Table 4 on page 53, and Table 5 on page 54. Therefore, Applicant submits that Table 6, on page 61, as well as the tables that follow Table 6, are consecutively labeled and Applicant respectfully requests that the Examiner withdraw this ground of objection.

In the Claims:

Claims 22-26 have been amended to clarify that the variant or fragment nucleic acids claimed encode a polypeptide that is overexpressed in lung and colon tumors. Support for amendment to Claims 22-26 may be found at pages 119-137.

Claim 35 has been amended to clarify that the claimed nucleic acid hybridizes under high stringency conditions. Support for this amendment may be found at page 30, lines 12-21 of the specification.

Claim Rejections:

35 U.S.C. § 101

The Examiner has rejected claims 22-41 under 35 U.S.C. 101 because allegedly the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The Examiner contends that the instant specification does not describe any biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner or any other specific feature that is associated with PRO347. Applicant respectfully disagrees. Applicant submits that several structural features, such as open reading frames, translation initiation sites, molecular weight and pI of the cDNA sequence of PRO347 are disclosed at lines 21-26 on page 103. At page 142, line 19, the specification discloses tissues where PRO347 nucleic acids are significantly expressed and where they are not.

Further, as the Examiner notes, the results of gene amplification experiments, which measure ΔCt values for PRO347 (one ΔCt unit is defined as corresponding to 1 PCR cycle or approximately a 2-fold amplification relative to normal), are presented in Table 10 on page 127. However, according to the Examiner, this table does not identify which columns of ΔCt values correspond to PRO347. Applicant respectfully disagrees. Specifically, at line 3 on page 127, each column is identified as corresponding to a particular PRO. More specifically, the fourth column from the right side of page 127 sets forth the ΔCt values, 1.315 and 1.525, for PRO347 in human colon tumor samples. Thus Applicant submits that the data demonstrates amplification of the PRO347 gene in primary tumors.

In fact, the Examiner noted that the specification discloses that nucleic acids encoding PRO347 have a ΔCt value of at least 1.0 for a number of primary lung and colon tumors and/or cell lines. However, the Examiner contends that it is not clear what the significance of such a ΔCt value would be. Applicant submits that this data (the ΔCt values) supports a diagnostic utility for nucleic acids, polypeptides and antibodies to

PRO347 and respectfully directs the attention of the Examiner to the declaration of Audrey D. Goddard, Ph.D., attached hereto as Appendix A ("the Goddard Declaration"). The Goddard Declaration makes it clear that skilled artisans recognize a well-established utility for the claimed invention at the time of filing.

Specifically, the Goddard Declaration illustrates the acceptance in the art of gene amplification data as an indicator of cancerous tissue. For example, in paragraph 7, Dr. Goddard specifically asserts her opinion that:

> [a]n at least 2-fold increase in gene copy number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that he detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number . . . as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology.

Goddard Declaration, paragraph 7.

The pending claims are directed to the nucleic acid encoding PRO, the amplified DNA sequences in the gene amplification experiments. The specification specifically asserts a utility for these nucleic acids. See, for example, page 137, lines 25-27, stating that "nucleic acid sequences encoding these polypeptides have utility as sources of nucleic acid probes for carrying out (the above) diagnostic procedures."

The Examiner indicated that the significance of a difference of 1 or 2 PCR cycles is not clear. The specification indicates that one ΔCt unit corresponds to 1 PCR cycle, or *approximately a 2-fold amplification relative to normal* (see page 120, lines 7-9). Furthermore, as indicated above, the Goddard Declaration indicates that a 2-fold increase in gene copy number is considered both significant and useful (see Goddard Declaration paragraph 7, and above). Thus, the Δ Ct data is indicative of relevant gene amplification.

The Examiner further indicates that, even if the data demonstrates a slight increase in copy number of PRO347 nucleic acids in primary tumors, such increase would not be indicative of a use of the encoded polypeptide as a diagnostic agent because cancerous tissue is known to be aneuploid. The Examiner asserts that the data presented in the

specification were not corrected for aneuploidy, and that a slight amplification of a gene does not necessarily mean over expression in a cancer tissue, but can merely be an indication that the tissue is aneuploid.

Applicant respectfully disagrees with this characterization. The data presented in the specification are from experiments using appropriate controls for aneuploidy (see, for example, page 137, lines 13-16). Applicant used framework mapping to control for aneuploidy and to ensure that the observed ΔCt data represent relevant gene amplification. Thus, the reported data are an indication of relevant gene amplification, and support the conclusion that PRO347, and related proteins and antibodies, can be used as a cancer diagnostic. Furthermore, considering the aneuploidy controls used by the Applicant, a skilled artisan would not be required to undertake undue experimentation to practice the claimed invention.

Considering these remarks, Applicant respectfully asserts that the claimed invention has utility and is fully enabled. Accordingly, Applicant requests that the Examiner reconsider and withdraw the rejections under § 101.

35 U.S.C. § 112, first paragraph

Claims 22-41 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement based on the Examiner's finding that the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Applicant submits that as explained above, claims 22-41 are supported by both a specific and substantial utility and a well established utility. Therefore, this ground of rejection has been overcome and Applicant respectfully requests that it be withdrawn.

Enablement

The Examiner has further rejected claims 22-41 under 35 U.S.C. 112, first paragraph, alleging that even if the specification were enabling of how to use the PRO347 nucleic acid, enablement would not be found commensurate in scope with the claims. Specifically, the Examiner contends that the specification does not enable one of skill in

the art to use fragments or variants that hybridize to SEQ ID NO:49. Applicant respectfully disagrees. Enablement is commensurate with the scope of the currently pending claims.

Applicant has amended Claims 22-26 to reflect that all claimed variant or fragment nucleic acids encode diagnostic encode polypeptides that are overexpressed in lung and colon tumors. One of skill in the art would appreciate therefore, that these variant and fragment nucleic acids would have the same diagnostic utility as the wild-type PRO347 polypeptide.

Further, at pages 59-62 of the specification, Applicant describes several methods for preparing or synthesizing variants and fragments of SEQ ID NO:49. One of skill in the art will recognize that many polypeptides, encoded by specific nucleic acids, have specific crucial amino acids, or active sites, and therefore many nucleic acids, encoding non-crucial amino acids, can be changed in a polypeptide sequence without substantially altering the physiological function or activity of that polypeptide. At page 61 of the instant specification, Applicant suggests several substitutions of nucleic or amino acids that may be made in various sequences, yet still conserve the structure and function of the encoded wild-type polypeptide. Furthermore, even significantly changing the amino acid or nucleic acid sequence of polypeptides will still result in polypeptides that retain many epitopes unique to the wild type polypeptide, allowing such variant and fragment polypeptides to be used to form specific antibodies to the various novel polypeptides. Therefore, Applicant submits that the skilled artisan would recognize that variants and fragments of PRO347 would have the same or at least similar utility to full length polypeptides in detecting, monitoring or preparing treatments for various cancers.

Furthermore, *a considerable amount of experimentation is permissible*, if it is merely routine, or *if the specification provides a reasonable amount of guidance* with respect to the direction in which the experimentation should proceed. *See In re Wands,* 858 F. 2d 731, 737 (Fed. Cir. 1988)(emphasis added). Moreover, according to the MPEP § 2164.01, "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."

Claims 27-35 have not been amended to clarify that the claimed nucleic acid encodes a polypeptide that is overexpressed in lung and colon tumors because these claims are directed to the wild-type nucleic acid sequence. Applicant has submitted a deposit of genetic material designated clone DNA44176-1244 with ATCC and assigned ATCC deposit No. ATCC 209532. A reference in the specification on page 148, line 3, to the deposit in the public depository which makes its contents accessible to the public satisfies the enablement requirement of 35 U.S.C. 112, first paragraph. *In re Argoudelis*, 143 F.2d 1390, 1392 (CCPA 1970).

For all of these reasons, Applicant respectfully requests that this ground of rejection be withdrawn.

Written Description

Claims 22-26 and 35-41 are rejected under 35 U.S.C. 112, first paragraph for failure to satisfy the written description requirement. The Examiner alleges that Claims 22-26 and 35-41 contain subject matter which is not described in the specification in such a way as to reasonable convey to one skilled in the art that the inventor, at the time of the application, had possession of the claimed invention. Applicant respectfully diagrees and submits that Claims 22-26 and 35-41 are adequately described in the present application. Applicant further submits that Applicant had possession of the claimed invention at the time of filing the application.

Applicant has amended Claims 22-26 to clarify that the claimed variant and fragment nucleic acids encompassed by Claims 22-26 and 38-41 encode a polypeptide that is overexpressed in lung and colon tumors. Therefore, Applicant submits that the nucleic acids of claims 22-26 and 38-41, having at least 80%, 85%, 90%, 95%, and 99% sequence identity to 1) the amino acid sequence of the polypeptide of SEQ ID NO:50; 2) the amino acid sequence of polypeptide of SEQ ID NO:50 lacking the signal peptide; 3) the amino acid sequence of the polypeptide of SEQ ID NO:50 encoding the extracellular domain; 4) the amino acid sequence of the polypeptide of SEQ ID NO:50 encoding the extracellular domain lacking the signal peptide; 5) the amino acid sequence of the

polypeptide encoded by the nucleic acid of SEQ ID NO:49; 6) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of SEQ ID NO:49, and 7) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA in ATCC Accession number 209532 satisfy the written description requirement.

The factors to be considered in determining whether an adequate written description has been set forth include (1) disclosure of complete or partial structure, (2) physical or chemical properties, (3) functional characteristics, (4) structure/function correlation, (5) methods of making the claimed product or any combination thereof. *See Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112 "Written Description" Requirement,* 66 Fed. Reg. 1099, 1106 (Jan.5, 2001). Applicant submits that the present application discloses a combination of the above elements required for an adequate written description and therefore sets forth an adequate written description of the claimed invention.

For example, the structure and sequence of the wild type nucleic acid encoding PRO347, encompassed by claims 27-35 are described throughout the specification. Even further and more specifically, at page 103, lines 1-29, the specification describes isolation of cDNA clones encoding human PRO347. Several structural features, such as open reading frames, translation initiation sites, molecular weight and pI of the cDNA sequence of PRO347 are disclosed at lines 21-26 on page 103. At page 142, line 19, the specification discloses tissues where PRO347 nucleic acids are significantly expressed and where they are not. At pages 59-62, the specification teaches how to prepare or synthesize PRO variants and fragments. At pages 119-137, the specification teaches that nucleic acids encoding PRO347 are overexpressed in lung and colon tumors and therefore are useful as diagnostic markers. The claims have been amended such that the claimed variant and fragment nucleic acids are required to have a sufficient sequence identity structure with the wild type nucleic acid sequence encoding PRO347, in addition to encoding a polypeptide that is overexpressed in lung and colon tumors.

Further, one of skill in the art will recognize that many polypeptides, encoded by specific nucleic acids, have specific crucial amino acids, or active sites, and therefore many non-

crucial amino acids can be changed in a polypeptide sequence without substantially altering the physiological function or activity of that polypeptide. At page 61 of the instant specification, Applicant suggests several substitutions of nucleic or amino acids that may be made in various sequences, yet still conserve the structure and function of the encoded wild-type polypeptide. Furthermore, even significantly changing the amino acid or nucleic acid sequence of polypeptides will still result in polypeptides that retain many epitopes unique to the wild type polypeptide, allowing such variant and fragment polypeptides to be used to form specific antibodies to the various novel polypeptides. Thus, Applicant respectfully submits that 80% sequence identity and greater for the claimed polypeptide, in addition to overexpression in lung and colon tumors, is sufficient to reasonably convey to one skilled in the relevant art that the Applicant, at the time the application was filed, had possession of the claimed invention.

Furthermore, Applicant has submitted a deposit of genetic material designated clone DNA44176-1244 with ATCC and assigned ATCC deposit no. ATCC 209532. A reference in the specification on page 148, line 3, to the deposit in the public depository which makes its contents accessible to the public constitutes an adequate description of the deposited material ... sufficient to comply with the written description requirement. *See Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 965 (Fed. Cir. 2002)

Finally, Claim 35 is directed to nucleic acids that hybridize to SEQ ID NOS: 49 and 50 under high stringency conditions. Such conditions are described at page 30, lines 12-21, and particularly at lines 17-21. Applicant describes at least at page 103, lines 2-29 and page 142, lines 1-24, using various oligonucleotide probes in hybridization reactions with various PRO347 sequences.

Claims 36-37 have been canceled and therefore the Examiner's rejection of these claims for failure to satisfy the written description requirement has been overcome.

Claims 38-41 are directed to a vector comprising the nucleic acid of Claim 22. Applicant submits that the nucleic acid of Claim 22 is adequately described as discussed above. Vectors, host cells and cell transformation are described at pages 64-68. Specifically,

Applicant describes production of PRO by culturing host cells transformed or transfected with a vector containing PRO nucleic acid. Even further, Applicant describes the expression of PRO polypeptides in *E.coli*, mammalian cells (CHO cells), and yeast on pages 111-115. The skilled artisan would understand that the described procedures could be carried out using PRO347.

For all these reasons, Applicant submits that the specification recites distinguishing, identifying characteristics, sufficient to satisfy the written description requirement with respect to claims 22-26 and 35-41. Applicant respectfully requests the Examiner withdraw this ground of rejection.

35 U.S.C. § 112, second paragraph

Claims 35-37 are rejected under 35 U.S.C. 112, second paragraph as being indefinite because the Examiner contends that "stringent" conditions may be low, moderate or high, causing the metes and bounds of the patent protection desired to be unclear.

As the Examiner notes, at page 30 of the instant specification, Applicant defines "stringent conditions" and "high stringency conditions." Also as the Examiner notes, Applicant provides exemplary hybridization and wash conditions as part of this definition. Applicant has amended Claim 35 to clarify that the claimed nucleic acid hybridizes under high stringency conditions. As explained at lines 17-21, page 30 of the specification, one example of high stringency conditions includes employing 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

Therefore, Applicant respectfully requests the Examiner withdraw this ground of rejection.

Priority Determination

The Examiner, based on her finding of lack of utility and enablement, alleges that the effective priority date for this application is 8/30/01. Applicant respectfully traverses this determination for at least the following reasons. Applicant has claimed priority to U.S. Application Serial No. 60/113,296, filed 12/22/1998, which discloses PRO347 (see Figure 14, SEQ ID NO: 14 and pages 50-51 of 60/113,296), as well as several specific, substantial, and credible utilities for the claimed nucleic acids encoding PRO347.

For example, 60/113,296 discusses using the claimed invention (1) as part of ribozyme and/or triple helix sequences which, in turn may be used in regulation of amplified genes at page 3, lines 23-25, (2) for determining the presence of PRO347 at lines 26-32 on page 3, and (3) for diagnosing a tumor by detecting the level of expression of a gene encoding PRO347 at lines 33-35 on page 3 - lines 1-24 on page 4. Further, at pages 23-28, 60/113,296 discusses detecting gene amplification/expression of PRO347 in certain tissues and at pages 28-29, 60/113,296 describes anti-PRO347 antibody binding studies.

Moreover, at pages 55-101, 60/113,296 describes methods for determining whether the genes encoding various PRO polypeptides are amplified in the genome of certain human lung, colon and/or breast cancers and/or cell lines. As with U.S. Application Serial No. 09/944,896, the gene amplification examples measure and discuss Δ Ct values. Further, the Goddard Declaration, discussed above, demonstrates that the skilled artisan would understand the significance of the Δ Ct value data discussed in the gene amplification studies.

Table 2, found at pages 65-72 sets forth the Δ Ct values for various PRO polypeptides in various tissues. The Δ Ct values for PRO347 are listed in the 8th column from the top, left-hand side of the page. This data demonstrates that the PRO347 gene is amplified in cancerous tissues. The results of the gene amplification study with respect

to PRO347 are discussed at page 105, lines 22-33. Amplification of PRO347 DNA was detected in various tumors and therefore, as stated at page 105, lines 32-33, "antagonists, (e.g. antibodies) directed against the protein encoded by DNA44176 (PRO347) would be expected to be useful in cancer therapy." Those of skill in the art would also recognize that the nucleic acid encoding the protein associated with cancer, as well as the protein itself would also have diagnostic utility.

For at least these reasons, Applicant submits that U.S. Application Serial No. 60/113,296 discloses specific, substantial and credible utilities for the claimed nucleic acids that encode PRO347. Applicant respectfully asserts that the proper priority date for the claimed invention is 12/22/1998, and requests that the Examiner reconsider the determination of priority.

35 U.S.C. § 102

Claims 22-26 and 35-41 are rejected under 35 U.S.C. 102(a) as being anticipated by Kato *et al.*, WO 01/49728, published July 12, 2001. Applicant has demonstrated that the proper priority date of the instant application is December 22, 1998, before Kato *et al* was published. Therefore, this ground of rejection has been overcome and Applicant respectfully requests that it be withdrawn.

Claims 22-41 are further rejected under 35 U.S.C. 102(b) as being anticipated by Botstein *et al*, WO 99/35170, July 15, 1999. As discussed above, Applicant has demonstrated that the proper priority date of the instant application is December 22, 1998, also before Botstein was published. Therefore, this ground of rejection has also been overcome and Applicant respectfully requests that it be withdrawn. Applicant also notes that Botstein *et al* is a Genentech application, filed the same day as provisional application 60/113,296, to which Applicant has demonstrated it is entitled to priority. Applicant further notes that the priority application, 60/113,296, has the same specification as the reference cited by the Examiner, Botstein *et al.*

Claims 22-26, 35, 36, 38, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by EST Database Accession No. AI792411, July 2, 1999. As discussed

above, Applicant has demonstrated that the proper priority date of the instant application is December 22, 1998, also before Accession No. AI792411 was published. Therefore, this ground of rejection has also been overcome and Applicant respectfully requests that it be withdrawn.

Claims 22-27, 31, 33, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Holtzman, WO 99/54343, published October 28, 1999. As discussed above, Applicant has demonstrated that the proper priority date of the instant application is December 22, 1998, also before Holtzman was published. Therefore, this ground of rejection has also been overcome and Applicant respectfully requests that it be withdrawn.

Claims 35-37 are rejected under 35 U.S.C. 102(b) and 102(e) as being anticipated by EST Database Accession NO. AI307814, April 8, 1999 and Mitcham *et al.*, U.S. Patent No. 6468546, filed 9/24/99. As discussed above, Applicant has demonstrated that the proper priority date of the instant application is December 22, 1998, also before AI307814 and Mitcham were published. Therefore, this ground of rejection has also been overcome and Applicant respectfully requests that it be withdrawn.

Finally, Claims 35-37 are rejected under 35 U.S.C. 102(b) as being anticipated by GenEMBL Database Accession No. HSU22027, Jan. 1, 1997. The Examiner notes that from nucleotides 1634-1654, No. HSU22027 is 100% identical to SEQ ID NO:49. However, Applicant has attached hereto as Appendix B an alignment of the two sequences. The alignment demonstrates that the full-length sequences are only 47.12% similar. Claims 36 and 37 have been canceled and Claim 35 has been amended to clarify that hybridization occurs under high stringency conditions, specifically described on page 30 at lines 17-21. Applicant submits that HSU22027 does not anticipate Claim 35 as amended because it is not expected to hybridize to the nucleic acid of Claim 35 under high stringency conditions. Therefore, Applicant respectfully requests this ground of rejection be withdrawn.

SUMMARY

Applicant believes that currently pending Claims 22-35 and 38-41 are patentable. Applicant respectfully requests the Examiner grant early allowance of this application. The Examiner is invited to contact the undersigned attorney for Applicant via telephone if such communication would expedite this application.

Respectfully submitted,

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